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13. ABSTRACT *(Maximum 200 Words)*

This award supported studies examining associations between elements of energy balance and breast cancer risk. We examined the following factors in relation to breast cancer incidence: 1) early life physical activity and weight interactions in postmenopausal women; 2) age specific intentional weight loss; 3) method of weight loss. In this interview-based study, breast cancer cases were identified from statewide registries and controls were randomly selected from population lists. For the first analysis (4614 cases, 5817 controls), reductions in postmenopausal breast cancer risk associated with regular strenuous physical activity (GE 1/day) were greatest for women in the 4th quartile of body mass index at age 18 (OR=0.45, 95% CI 0.26-0.79). Also, compared to women with no activity and little adult weight gain, frequent physical activity as associated with a significant risk reduction in women who lost weight (OR=0.19, CI 0.05-0.70). For the next two analyses (2156 cases, 2833 controls) extensive weight loss history was ascertained. After adjustment, substantial intentional weight loss of lbs in the teens was associated with significant breast cancer risk reduction (OR=0.43, CI 0.19-0.99). Of the 13 weight loss methods reported, the most common method was low calorie diets (36%). None of the specific methods were independently associated with breast cancer risk.

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Patty A Newton 12/1/02

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INTRODUCTION

This postdoctoral training award supported studies designed to evaluate associations between elements of energy balance (physical activity, body size, intentional weight loss) and risk of breast cancer.

TECHNICAL OBJECTIVE 1 (PHYSICAL ACTIVITY)

Previously reported results from our population-based case-control study show that daily physical activity at 14-22 years of age is associated with a 50% reduction in breast cancer risk [1]. We completed analyses of effect modification by body size and weight change on the relation between early-life physical activity and breast cancer risk. This manuscript was published in *Cancer Epidemiology, Biomarkers and Prevention* 2000, 9:591-595 (Appendix C).

Results from this population-based case-control study indicate that the reduced risk of postmenopausal breast cancer associated with daily physical activity at 14-22 years of age may be greatest in women who were heaviest during the same time period or who, over the adult years, either lost weight or gained only modest amounts. Compared to women with no activity and little weight gain, frequent physical activity was associated with reduced breast cancer risk in women who had lost weight since age 18 (odds ratio=0.19, 95% confidence interval=0.05-0.70), who gained little weight (0-7.3 kg, odds ratio=0.36, 95% confidence interval=0.15-0.85) or who gained modest amounts of weight (7.4-15.0 kg, odds ratio=0.31, 95% confidence interval=0.11-0.66).

These findings suggest that daily physical activity during young adulthood may have the greatest benefit for reducing postmenopausal breast cancer risk among women who avoid substantive weight gain during adult life. In contrast, a protective effect of early-life physical activity may not exist in postmenopausal women who experience appreciable weight gain. Given the disturbing trends of an increasing prevalence of overweight/obese adults [2] and children [3, 4] in the United States, and of increasing prevalence of physical inactivity among girls [5], these findings may be relevant for future breast cancer prevention efforts.

TECHNICAL OBJECTIVE 2 (INTENTIONAL WEIGHT LOSS)

A manuscript describing these results will be submitted. A summary follows, below.

Study participants and design

All female residents of Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire, who had a new diagnosis of invasive breast cancer and were less than 70 years of age, were eligible for this study. Case women were identified by each state's cancer registry from July 1996 through July 1998. Permission was obtained from each physician of record to interview eligible patients. Eligibility was limited to women with listed telephone numbers, drivers' licenses verified by self-report (if less than 65 years of age), and known dates of diagnosis. This on-going study has enrolled 2,156 cases, which represents approximately 80% of the eligible cancer patients.

Control subjects were selected from the community using two sampling frames: women under 65 years of age were selected from a list of licensed drivers, and women aged 65-69 years of age were selected from a roster of Medicare beneficiaries compiled by the Health Care Financing

Administration. Updated computer files of potential controls were obtained annually. Controls were selected at random withing age strata to yield an age distribution similar to that of the cases within each state. Controls had no personal history of breast cancer, a listed telephone number, and, if less than 65 years of age, a driver's license (by self-report). This study has enrolled 2,833 controls which represents approximately 80% of eligible control subjects.

Data collection

Letters were sent to eligible study participants briefly describing the study before contacting them by telephone. The 45 minute telephone interview elicited information on lifetime physical activity, lifetime occupations, reproductive experiences, personal and family medical history, and demographic factors. Intentional weight loss was assessed with the following questions:

- Did you ever lose at least 10 pounds on purpose?
- If yes, Did you lose at least 10 pounds or more on purpose during [your teens, your twenties...during each decade of life and for the year prior to the reference age]?
- If yes, How many times did you lose 10 pounds or more?
- How much did you lose, on purpose, the [first, second, third, fourth] time?

Information on weight at each decade, weight one year prior to the reference age ('recent' weight), height at age 25, and height one year prior to the reference age was also obtained.

Statistical analysis

Intentional weight loss was expressed in several ways: as a dichotomous variable (yes/no) at each age period, as the number of episodes of weight loss at each age period, as the cumulative number of episodes of intentional weight loss, as the total amount of weight loss at each age period, and as the cumulative amount of weight loss over all age periods.

The reference age for cases was defined as their age at diagnosis. A comparable reference age for controls was defined as the median date of diagnosis for similarly-aged cases (within 5-year age strata) interviewed during the same month. Recent body mass index (BMI) (recent weight (kg) / tallest height (m^2)) was calculated and categorized into quintiles based on the distribution of control subjects. BMI at age 18 was calculated using weight at age 18 and tallest height (weight-age 18 (kg) / tallest height (m^2)). Weight change (difference between weight at age 18 and recent weight) was separated into one category of weight loss and tertiles of weight gain, with cut-points defined by the control distribution.

Odds ratios (OR) and 95 percent confidence intervals (CI) were obtained from unconditional logistic regression models [6]. All models were adjusted for age (7 levels), state (3 levels), parity (4 levels), menopausal status, family history of breast cancer, and recent BMI (5 levels). Models evaluating cumulative number of weight loss episodes included weight change (4 levels) and BMI at age 18. Stratified analyses according to weight change included BMI at age 18 as a covariate. Women with missing values for covariates were assigned to separate categories and retained in all analyses.

Reliability substudy

To assess the reliability of the intentional weight loss questions, we re-interviewed a sequential sample of cases and controls initially interviewed in Wisconsin during October 1998. After an average of 9.5

months (range 8 -11 months), 118 cases (out of 126 possible, 94%) and 82 controls (out of 90 possible, 91%) were successfully re-contacted and re-interviewed. Kappas and 95 percent lower confidence limits (LCL) were estimated to evaluate the reproducibility of the intentional weight loss items [7]. Among women interviewed a second time, reproducibility of the interview was high (Table 1, Appendix D). The kappa for ever reporting intentional weight loss of at least ten pounds was 0.70 (LCL 0.56) for cases and 0.73 (LCL 0.57) for controls. The kappas for recall of intentional weight loss appeared greatest for intentional weight loss occurring during the teenage years (cases 0.80, LCL 0.64; controls 0.68, LCL 0.45), with moderate kappa values for the subsequent decades including the previous one (cases 0.56, LCL 0.41; controls 0.62, LCL 0.45).

Results

Women who reported ever losing at least 10 pounds on purpose tended to be younger, heavier and had greater amounts of weight gain than women who reported no intentional weight loss (Table 1, Appendix E). The association between intentional weight loss and breast cancer risk was null (Table 2, Appendix E). However, a 22% reduction in breast cancer risk was observed for those women intentionally losing weight in their teens, compared to women who never intentionally lost weight (OR=0.78, CI=0.64-0.96). For all other time periods, including the year prior to the reference date, null associations between intentionally losing weight and breast cancer risk were observed.

Associations between breast cancer risk and the number of times weight was lost are shown in Table 3 (Appendix E). Among subjects reporting ever intentionally losing at least 10 pounds, a reduced odds of breast cancer was observed for women reporting one (OR=0.78, CI=0.61-0.98) and two (OR=0.65, CI=0.42-0.99) weight loss episodes during their teens. Losing weight three times during this time period was not associated with risk. An increased risk of breast cancer was observed among women reporting losing weight only one time during their thirties (OR=1.29, CI=1.08-1.55); no associations were observed with a greater number of weight loss episodes. Estimates for the number of episodes of intentional weight loss were close to the null for all other age periods. For the cumulative number of weight loss episodes, elevated odds were observed for four and five episodes of intentional weight loss (OR=1.32, CI=0.98-1.78 and OR=1.21, CI=0.83-1.76, respectively).

Amount of intentional weight loss and risk of breast cancer in women who ever lost at least 10 pounds on purpose is shown in Table 4 (Appendix E). During the teens, lower odds of breast cancer were observed for each category of weight loss, compared to not losing weight intentionally at this age (10-29 pounds OR=0.57, CI=0.38-0.85; 30-59 pounds OR=0.35, CI=0.19-0.67; ≥60 pounds OR=0.43, CI=0.19-0.99). An inverse association between weight loss and breast cancer risk was also observed for weight loss during the forties (40-69 pounds OR=0.60, CI=0.36-1.00; ≥70 pounds OR = 0.64, CI = 0.34-1.17; p-trend = 0.07). Cumulative weight loss was also inversely associated with risk of breast cancer; the highest amount of cumulative weight loss (≥120 pounds) was associated with a 43% reduction in risk (OR=0.57, CI=0.37-0.89, p-trend=0.01).

Cumulative intentional weight loss and breast cancer risk were stratified by weight change since age 18 (Table 5, Appendix E). Cumulative amounts of intentional weight loss were inversely associated with breast cancer risk in women in the third tertile of weight gain (weight gain > 17.7 kg, p-trend=0.04). In this group, cumulative weight loss of at least 120 pounds was associated with a 49% reduction in risk, independent of the cumulative number of times weight was lost (OR=0.51, 95% CI=0.27-0.98).

Discussion

In this large study, both the number of intentional weight loss episodes and the amount of weight lost during the teen years were associated with a reduction in breast cancer risk. A higher number of cumulative weight loss episodes appeared to be associated with an increased risk of breast cancer. However, increasing amounts of weight loss during the thirties, forties and cumulatively was associated with reductions in risk independent of the number of weight loss episodes and attained body size. Increasing amounts of cumulative weight loss appeared to be most beneficial in women who gained substantial amounts of weight.

Previous studies have shown that weight loss is inversely associated with risk of breast cancer [8, 9]. However, we are not aware of any studies that have directly addressed whether intentional weight loss (not disease-related weight loss) was associated with breast cancer risk. In one study, a reduction in breast cancer mortality associated with intentional weight loss was observed in women with obesity-related disorders [10]. However, this finding is not generalizable to breast cancer incidence. Distinguishing between intentional and disease-related weight loss, as well as identifying other patterns associated with intentional weight loss such as weight cycling, may further clarify the association between risk of breast cancer and intentional weight loss.

Few studies have examined the risk of breast cancer associated with weight cycling. Trentham-Dietz et al. [11] showed that weight cycling (weight loss of at least 20 pounds with regain of half the amount lost) was not associated with postmenopausal breast cancer risk independent of attained body size and weight gain. These results are in general agreement with our observation that frequent episodes of intentional weight loss of at least ten pounds was not associated with breast cancer risk at later age periods. It has been hypothesized that multiple episodes of weight loss with regain may be detrimental to health through pathophysiologic alterations in macronutrient metabolism, body composition or preference for high fat foods. However, weight cycling does not appear to be associated with elevated levels of fasting blood glucose or insulin, dyslipidemias, or other measures of fat metabolism [12-15]. Associations with female endogenous hormones are unclear.

Data presented here suggest that, in women who are not successful at maintaining intentional weight loss but experience substantial amounts of weight gain, large amounts of intentional weight loss may associated with a reduced of odds of breast cancer. This is an important observation given the strong and consistent evidence that weight gain increases the risk of developing postmenopausal breast cancer [8, 16, 17]. Because weight gain may increase exposure to endogenous estrogen [20-22], multiple episodes of weight loss may interrupt this exposure by decreasing circulating estrogen levels or preventing increases.

Limitations of our study should be considered when the interpreting the results. High response rates of cases and controls make substantial selection bias unlikely. However, recall bias may be present due to our study's dependence on self-reports of intentional weight loss. Although recall bias may be a potential limitation, the reports themselves are likely reliable. As discussed above, reproducibility of the interview was high.

Intentional weight loss is a common behavior among American women, particularly those that are overweight or obese [23] and encompasses a complex set of weight change patterns. These results suggest that repeated episodes of intentional weight loss may be detrimental with regard to breast

cancer prevention, whereas large amounts of weight loss, particularly in women who had substantial weight gain, may be beneficial. The underlying biological mechanisms of these findings are not clear. Examining these associations in the context of how weight loss was achieved may help to clarify these results (see Technical Objective 3). Additionally, further analysis in sub-groups of women defined by such factors as attained body size, menopausal status and hormone replacement therapy use, may be informative.

TECHNICAL OBJECTIVE 3 (WEIGHT LOSS METHODS)

A manuscript describing the results of our evaluation of specific weight loss methods and breast cancer risk is in preparation. A summary follows below.

Study participants and design

All female residents of Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire, who had a new diagnosis of invasive breast cancer and were less than 70 years of age, were eligible for this study. Case women were identified by each state's cancer registry from July 1996 through July 1998. Permission was obtained from each physician of record to interview eligible patients. Eligibility was limited to women with listed telephone numbers, drivers' licenses verified by self-report (if less than 65 years of age), and known dates of diagnosis. This on-going study has enrolled 2,156 cases, which represents approximately 80% of the eligible cancer patients.

Control subjects were selected from the community using two sampling frames: women under 65 years of age were selected from a list of licensed drivers, and women aged 65-69 years of age were selected from a roster of Medicare beneficiaries compiled by the Health Care Financing Administration. Updated computer files of potential controls were obtained annually. Controls were selected at random withing age strata to yield an age distribution similar to that of the cases within each state. Controls had no personal history of breast cancer, a listed telephone number, and, if less than 65 years of age, a driver's license (by self-report). This study has enrolled 2,833 controls which represents approximately 80% of eligible control subjects.

Data collection

A 45-minute telephone interview elicited information on lifetime physical activity, occupation, reproductive experiences, personal and family medical history, and demographic factors.

Information on weight at each decade, weight one year prior to reference age ("recent weight") and height was also obtained.

To assess weight loss method for each episode of intentional weight loss, the following questions were included in the study interview.

- [for each weight loss episode]: What methods did you use [up to two, from list]
- [list of weight loss methods: low calorie diet, low fat diet, skipped meals, over-the-counter diet pills, commercial weight loss program, prescription medication, exercise, laxatives or water pills, gastric surgery, regurgitation]

Statistical analysis

Methods of weight loss were defined for each weight loss episode. The reference age for cases was defined as their age at diagnosis. A comparable reference period for controls was defined as the median date of diagnosis for similarly aged cases interviewed within the same month.

Odds ratios and 95% confidence intervals (CI) were obtained from unconditional logistic regression models [6] for each method of weight loss. All estimates were adjusted for age (7 levels), state (3 levels), parity (4 levels), menopausal status, family history of breast cancer, and recent BMI (5 levels). Stratified analyses were used to examine the effect of the various methods of weight loss.

Reliability substudy

As described above for Technical Objective 2, we conducted a reliability substudy using a sequential sample of 188 breast cancer cases and 76 controls initially interviewed in Wisconsin during October 1998. Kappas and 95% confidence intervals were estimated to evaluate the reproducibility of the intentional weight loss methods (Table 2, Appendix D). While kappas for the most commonly reported method—low calorie diet—were modest (0.46 cases, 0.42 controls), the kappas for the second most common method—commercial weight loss program—were high (0.69 cases, 0.76 controls). Kappas were also moderate for exercise, the third most commonly reported method of intentional weight loss (0.49 cases, 0.62 controls).

Results

The frequencies of each weight loss method by disease status is shown in Table 6 (Appendix E). The most common weight loss method was a low calorie diet (36% for cases and controls). The OR associated with each method was about 1.00 (Table 6).

Stratified analyses were conducted of the three most common methods of intentional weight loss according to other variables. There was a suggestion that a low calorie diet (OR = 0.77, CI 0.63-0.99) and exercise (OR = 0.78, CI 0.60-1.01) were associated with breast cancer risk among women who gained little weight since age 18 (Table 7, Appendix E). The associations between methods of loss and breast cancer risk were null when limited to women who lost weight or gained appreciable weight (≥40 pounds).

The null association between method of intentional weight loss and breast cancer risk was not modified by the magnitude of the average loss per episode (Table 8, Appendix E) or the timing of the weight loss (Table 9, Appendix E). A modest reduction in risk was observed for women who reported a low calorie diet with substantial average weight loss (≥20 pounds; OR = 0.81, CI 0.66-1.00), as compared to women who reported never intentionally losing weight.

Discussion

In this large study, no method of intentional weight loss was associated with breast cancer risk. Statistical power was limited, however, to evaluate specific weight loss methods except for low fat, commercial weight loss programs and exercise. The data were suggestive of a 20% reduced risk of breast cancer confined to women using a low calorie diet who intentionally lost higher amounts of weight (>20 pounds), or who gained little weight throughout adulthood (<20 pounds).

Intentional weight loss is a common behavior among American women [10], indeed, we found that about 60% of women 20-69 reported at least one attempt to lose 10 or more pounds. Previous studies, including our own, have shown that weight loss is inversely associated with breast cancer risk [8, 11], however, the means by which weight loss is achieved has not been investigated with .respect to breast cancer. Among women who intentionally lose weight, differential effects of increased energy expenditure (physical activity) and restriction (dieting) on breast cancer incidence may exist. Such effects may be possibly mediated by differing influences on body composition, particularly fat stores. Several clinic-based studies have found that weight loss due to exercise (alone or in combination with energy restriction) results in greater losses of body fat compared to energy restriction alone [30-34]. While we did not observe a relation with weight loss effected by exercise alone, even among women who achieved and/or maintained substantial weight loss, our assessment of the nature of that exercise (e.g. METs and duration) was very limited. A more complete evaluation of exercise and weight loss will be possible in conjunction with our analysis of lifetime recreational and occupational physical activity that was ascertained in our full study interview. We did find that low calorie diets were associated with modestly reduced risk when substantial weight loss and/or maintained throughout adulthood. This may suggest an effect of low calorie diets per se, or instead, may be due to the fact that this was the most common and practically maintained behavior.

Despite the of lack of conclusive evidence from our analysis, we believe that differential effects of exercise, dieting, or both on body composition may be important in supporting hypotheses relating different patterns of association between body mass and breast cancer risk in pre- and postmenopausal women [35]. One proposed mechanism to account for the different observations in pre- and postmenopausal women is that obese premenopausal women are more likely to have longer menstrual cycle lengths and a greater tendency for anovulatory cycles, resulting in a lower net estrogen influence on target breast cells [36-41]. Estrogens derived from androgenic steroids in adipose tissue may account for the increased risk of breast cancer in postmenopausal obese women [18]. Thus, risk of breast cancer may be lower in women who achieve weight loss primarily through exercising or exercising with dieting due to effects on levels of body fat relative to weight loss achieved through dieting alone.

While our study was large, we were limited by the number of women who attempted weight loss by some of the methods, and by the amount of weight loss that was successfully maintained. Further, our information on some of the methods, notably exercise, may have been too abbreviated to correctly classify women. Such misclassification would tend to attenuate any effect. Reassuringly, however, selection bias is unlikely, given our high participation rates, and the reports appear to be reliable.

In summary, specific weight loss methods, as evaluated in our study, did not appear to be associated with breast cancer risk, although low calorie diets were inversely associated with risk when the weight loss was substantial and/or maintained throughout adulthood. Further analysis of women by menopausal status (and possibly hormone use) may provide additional insight into the relation between weight, weight loss and breast cancer risk.

OTHER ACTIVITIES

As a complement to the above analyses we also examined the association between physical activity and endometrial cancer risk. Endometrial cancer is a hormone-mediated tumor with recent exogenous

and endogenous risk factors including use of hormone replacement therapy, smoking and obesity [24-29]. We hypothesized that if the effect of physical activity on cancer risk was via hormone suppression, endometrial cancer incidence would also be reduced in women. Our results support this hypothesis. We found that recent moderate and vigorous physical activity were associated with a 22% and 29% reduction in endometrial cancer risk, respectively. A manuscript describing this study has been submitted (Appendix F). We also examined the association between diabetes, obesity and endometrial cancer (*American Journal of Epidemiology* 1998, 148:240-251, Appendix G). We found both diabetes and weight were independent risk factors for endometrial cancer.

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APPENDICES

Appendix A: List of key research accomplishments.

- Publication of "Early Life Physical Activity and Postmenopausal Breast Cancer: Effect of Body Size and Weight Change" in *Cancer Epidemiology, Biomarkers and Prevention.*
- Publication of "Diabetes, Body Size and Endometrial Cancer Risk" in *American Journal of Epidemiology.*
- Submission of paper titled "Recreational Physical Activity and Risk of Endometrial Cancer."
- Design and implementation of assessments of weight loss methods and completion of reliability substudy of intentional weight loss questions.
- Analysis on intentional weight loss and risk of breast cancer.
- Analysis of method of weight loss and risk of breast cancer.

Appendix B: List of reportable outcomes.

- Publication: "Early Life Physical Activity and Postmenopausal Breast Cancer: Effect of Body Size and Weight Change".
- Tables describing relations between intentional weight loss and breast cancer risk.
- Table showing results from reliability sub-study of intentional weight loss.
- Tables showing results of weight loss methods and breast cancer risk.

Appendix C

Early-Life Physical Activity and Postmenopausal Breast Cancer: Effect of Body Size and Weight Change[1]

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Abstract

It is not yet known whether early-life physical activity reduces the risk of developing breast cancer. Subgroup analyses according to menopausal status and body mass may help clarify this association. Data from a population-based case-control study of female residents of Wisconsin, Massachusetts, Maine, and New Hampshire were used to examine associations between body mass and breast cancer risk. Cases (n = 4614) were identified by each state's tumor registry; controls (n = 5817) were randomly selected from population lists. Frequency of participation in strenuous physical activity when 14–22 years of age, weight at age 18 and 5 years before interview, height, and other factors were ascertained through structured telephone interviews. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed using logistic regression. Reductions in postmenopausal breast cancer risk associated with strenuous physical activity were greatest for women in the fourth quartile of body mass index at age 18; the OR for women with the highest activity frequency on average (≥once/day) was 0.45 (95% CI = 0.26–0.79). Associations with frequency of activity also varied by weight change. Compared to women with no activity and little adult weight gain, frequent physical activity was associated with reduced postmenopausal breast cancer risk in women who had lost weight since age 18 (OR = 0.19, 95% CI = 0.05–0.70) or had gained little or modest amounts of weight (weight gain: first tertile, OR = 0.36, 95% CI = 0.05–0.85; second tertile, OR = 0.31, 95% CI = 0.14–0.66). Weighted MET score analyses yielded similar but less inverse results. These findings suggest that the reduced risk of postmenopausal breast cancer associated with frequent, early-life physical activity may be greatest in women who, over the adult years, either lost weight or gained only modest amounts.

Introduction

Most epidemiological studies of physical activity report a reduction in the risk of breast cancer, although the results are not completely consistent (1, 2). In a prospective study of Norwegian women, Thune *et al.* (3) observed that the reduced risk of breast cancer associated with higher levels of recreational physical activity during midlife was greatest in lean women. This finding suggests that analyses in subgroups defined by measures of body mass may provide a clearer understanding of the role of physical activity in the prevention of postmenopausal breast cancer where the adverse effects of obesity are observed (4). High levels of energy expenditure have been correlated with a lower percentage of adipose tissue (5–9), the primary source of endogenous estrogen after menopause (10). Thus, simultaneous examination of body mass, physical activity, and breast cancer risk may help elucidate the mechanisms underlying an inverse association.

The purpose of this report is to expand on our previous observation of a reduced risk of breast cancer associated with regular, moderate-to-strenuous activity in early life (11) by evaluating whether reductions in postmenopausal breast cancer risk depend on body size at age 18 and at interview.

Materials and Methods

Study Participants and Design. Detailed descriptions of this case-control study have been reported (11). Briefly, all female residents ages 20–74 years of Wisconsin, Massachusetts (excluding metropolitan Boston), Maine, and New Hampshire who had a new diagnosis of invasive breast cancer were potentially eligible for this study. Case women were identified by each state's cancer registry from April 1988 through December 1991, except for New Hampshire, where women were enrolled beginning in January 1990. Eligibility was limited to women with listed telephone numbers and drivers' licenses (if less than 65 years of age). Of the 8532 eligible cases, physicians refused contact for 709 cases (8.3%); 464 cases (5.4%) were deceased, 69 cases (0.8%) could not be located, and 402 cases (4.7%) refused to participate. The overall response rate for cases was 80.7%.

Control subjects were randomly selected from the community using two sampling frames: (*a*) women less than 65 years of age were selected from lists of licensed drivers; and (*b*) women ages 65–74 years were selected from a roster of Medicare beneficiaries compiled by the Health Care Financing

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Administration. Eligible controls had no personal history of breast cancer, a listed telephone number, and, if less than 65 years of age, a driver's license. Of the 11,329 eligible controls, 122 (1.1%) had died, 153 (1.4%) could not be located, and 1,521 (13.4%) refused to participate, leaving 9,529 (84.2%) women for analysis.

Data Collection. A telephone interview elicited information on participation in any strenuous physical activity, reproductive history, personal and family medical history, and demographic factors. Strenuous physical activity or team sport participation was ascertained for two age periods: (*a*) 14 to <18 years; and (*b*) 18–22 years. Interviewers were instructed to include only strenuous activities (above MET[3] 6; Ref. 12) such as basketball, soccer, and swimming as well as labor, but not high school physical education. Up to three strenuous activities and/or sports were recorded for each time period, and for each reported activity, the number of years, the number of months per year, and the frequency of episodes (per day/week/month) of participation were noted. We did not ascertain the length (minutes) of each episode of activity. Information on weight 5 years before interview ("recent weight") and tallest height were obtained. For interviews after August 1988, women were also asked about their weight at age 18.

Statistical Analysis. Women were classified as postmenopausal if they reported natural menopause or bilateral oophorectomy before their reference age, which, for cases, was their age at diagnosis. A comparable reference age for controls was defined as the age at interview minus the average time from diagnosis to interview for the case group within each state (range, 8–21 months). Women who reported hysterectomy alone and with at least one remaining ovary were classified as postmenopausal if their age at surgery was in the highest decile for age at natural menopause in the control group (≥55 years for smokers and ≥56 years for nonsmokers).

The frequencies of episodes of reported strenuous physical activities were summed for each time period (14–18 and 18–22 years) and expressed as the number of times per year subjects engaged in physical activity. Frequency of physical activity was then averaged across the two time periods and categorized into five levels. Each physical activity was classified by the average rate of energy expenditure and defined as the ratio of work metabolic rate to resting metabolic rate (MET score; Ref. 12). Weighted MET scores were also calculated as the frequency of activity for each time period multiplied by the MET scores of each activity (11).

Quartiles of BMI [recent weight (kg)/tallest height (m^2)] were calculated based on the distribution of control subjects. Four levels of weight change (difference between recent weight and weight at age 18) were defined: (*a*) weight loss (weight change < 0); and (*b*) tertiles of weight gain (weight change ≥ 0) based on the distribution of controls.

ORs and 95% CIs were obtained from conditional logistic regression models stratified according to age and state (13). To evaluate the joint effects of physical activity and weight variables, indicator variables representing the joint classification of frequency of activity and BMI at age 18, BMI 5 years before interview (recent BMI), and weight change were constructed. All models were adjusted for parity, age at first birth, age at menarche, family history of breast cancer, education, and age at menopause. Additional adjustment for other variables including smoking or alcohol history and use of exogenous hormones did not materially affect risk estimates. Additionally, weight at age 18 was included when evaluating recent BMI, and BMI at age 18 was included when evaluating associations within weight change strata. Effect modification by BMI at age 18, recent BMI, and weight change was evaluated by examining the difference in the log-likelihood between models with and without interaction terms expressed as the products of continuous variables. Women with missing values for covariates were assigned to unknown categories and retained in all analyses.

Subjects with missing or incomplete information on physical activity (256 cases and 428 controls), menopausal status (260 cases and 378 controls), and weight (recent weight and weight at age 18) or height (219 cases and 312 controls) were excluded, therefore limiting analyses to 6186 cases and 8452 controls. Analyses were further restricted to postmenopausal subjects (4614 cases and 5817 controls) because the adverse effect of obesity was present only in this group (14), and the number of premenopausal cases (n = 1572) was too small for separate examination of interactions with high levels of activity.

Table 1 ORs and 95% CIs of postmenopausal breast cancer according to frequency of early life physical activity, BMI, and weight change

	Cases (n = 4614)	Controls (n = 5817)	OR (95% CI)
Frequency of activity (times/year)[a]			
0	2969	3600	1
1–47	825	1085	0.94 (0.85–1.05)
48–103	368	497	0.93 (0.80–1.08)
104–363	397	531	0.90 (0.78–1.04)
≥364	55	104	0.55 (0.39–0.78)
			P for trend = 0.002
Weighted MET score[b]			
0	2969	3600	1
1–2	561	696	0.95 (0.83–1.08)
3–4	694	957	0.91 (0.81–1.02)
5–12	390	564	0.86 (0.74–0.99)
			P for trend = 0.01
BMI (quartiles)			
BMI at age 18 (kg/m^2)[c]			
<18.6	1191	1451	1
18.7–20.1	1173	1456	0.97 (0.97–1.09)
20.2–21.8	1094	1437	0.89 (0.79–1.00)
>21.8	1156	1473	0.92 (0.82–1.03)
			P for trend = 0.05
Recent BMI (kg/m^2)[c]			
<21.8	1035	1478	1
21.9–23.8	1043	1435	1.06 (0.94–1.19)
23.9–26.5	1147	1438	1.11 (0.99–1.25)
>26.5	1389	1466	1.33 (1.18–1.49)
			P for trend < 0.001
Weight change (kg)[d]			
<0	326	537	0.89 (0.75–1.05)
0–7.3	1181	1710	1
7.4–15.0	1361	1777	1.12 (1.00–1.29)
>15.0	1746	1793	1.40 (1.26–1.56)
			P for trend < 0.001

[a] Physical activity estimates adjusted for BMI at age 18, age at first full-term pregnancy, parity, age at menarche, family history of breast cancer, education, and age at menopause.
[b] Weighted MET score was calculated as the average ratio of work metabolic rate to resting metabolic rate, multiplied by the relative frequency of the specific activities reported by each participant.
[c] BMI estimates adjusted for frequency of physical activity and the other covariates listed above.
[d] Weight change estimates adjusted for frequency of physical activity, BMI at age 18, and the other covariates listed above.

[3] The abbreviations used are: MET, ratio of work metabolic rate to resting metabolic rate; OR, odds ratio; CI, confidence interval; BMI, body mass index.

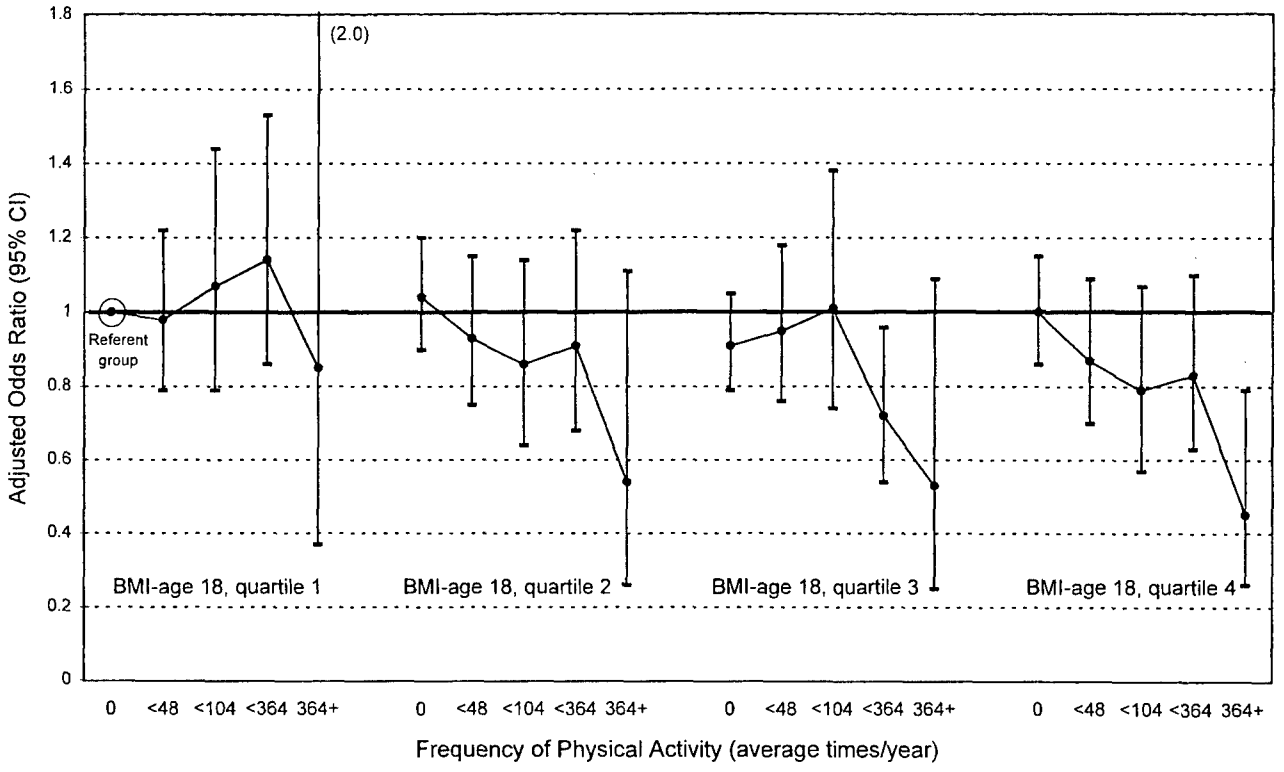

Fig. 1. Adjusted ORs of postmenopausal breast cancer according to BMI at age 18 (*BMI-age 18*) and frequency of physical activity at 14–22 years of age.

Results

Frequent (≥once/day on average) strenuous physical activity at age 14–22 years was associated with up to a 45% reduction in risk of postmenopausal breast cancer (OR = 0.55, 95% CI = 0.39–0.78, P for trend = 0.002; Table 1). The association between weighted MET score and risk of postmenopausal breast cancer was not as strong (P for trend = 0.01). A weak inverse trend between BMI at age 18 and postmenopausal breast cancer risk was observed (P for trend = 0.05), whereas a strong, positive association was observed with recent BMI (P for trend < 0.001). Weight change between 18 years of age and 5 years before interview was positively associated with breast cancer risk (P for trend < 0.001), with an OR of 1.40 (95% CI = 1.26–1.56) for the highest tertile of weight gain compared to the lowest tertile.

The relationship between strenuous physical activity and risk of postmenopausal breast cancer varied according to BMI at age 18 (Fig. 1; P for interaction = 0.02). Reductions in risk were most consistently observed in women with greater BMI at age 18. Compared with subjects in the first quartile of BMI at age 18 who reported no activity, the OR for women in the fourth quartile of BMI at age 18 who exercised on average ≥364 times/year was 0.45 (95% CI = 0.26–0.79). Similar but less strong results were obtained when weighted MET scores were evaluated (P for interaction = 0.08).

Associations between strenuous physical activity and postmenopausal breast cancer risk also varied by weight change between age 18 and 5 years before interview (Fig. 2; P for interaction = 0.03). Among those who lost weight, the OR for the highest frequency of activity was 0.19 (95% CI = 0.05–0.70) compared to no activity in the first tertile of weight gain. In the first tertile of weight gain, a significantly lower risk of postmenopausal breast cancer was associated with frequent activity (≥364 times/year; OR = 0.36; 95% CI = 0.15–0.85; P for trend = 0.001) compared to no activity. In the second tertile of weight gain, a lower risk of breast cancer was observed only with the highest frequency of strenuous activity (OR = 0.31; 95% CI = 0.11–0.66), compared to no activity in the first tertile of weight gain. Strenuous physical activity was not associated with breast cancer risk in the highest tertile of weight gain. Weighted MET score results were again similar but were less strongly inverse (P for interaction = 0.3).

Additionally, effect modification of recent BMI on the relationship between frequency of strenuous physical activity and postmenopausal breast cancer was not evident (P for interaction = 0.48).

Discussion

Results from this study suggest that the reduced risk of postmenopausal breast cancer associated with frequent episodes strenuous physical activity at 14–22 years of age may be greatest in women who were heaviest within the same time period or who, over the adult years, either lost weight or gained only modest amounts. Among women who were heaviest at age 18, risk of postmenopausal breast cancer was reduced by about 50% in those who exercised frequently.

More pronounced were results obtained from the model examining the joint effects of early-life physical activity and weight change between age 18 and 5 years before interview. Risk of postmenopausal breast cancer was reduced by about 80% among women who were active on a very frequent basis as young adults and who had lost weight between age 18 and 5 years before interview, independent of initial weight. However,

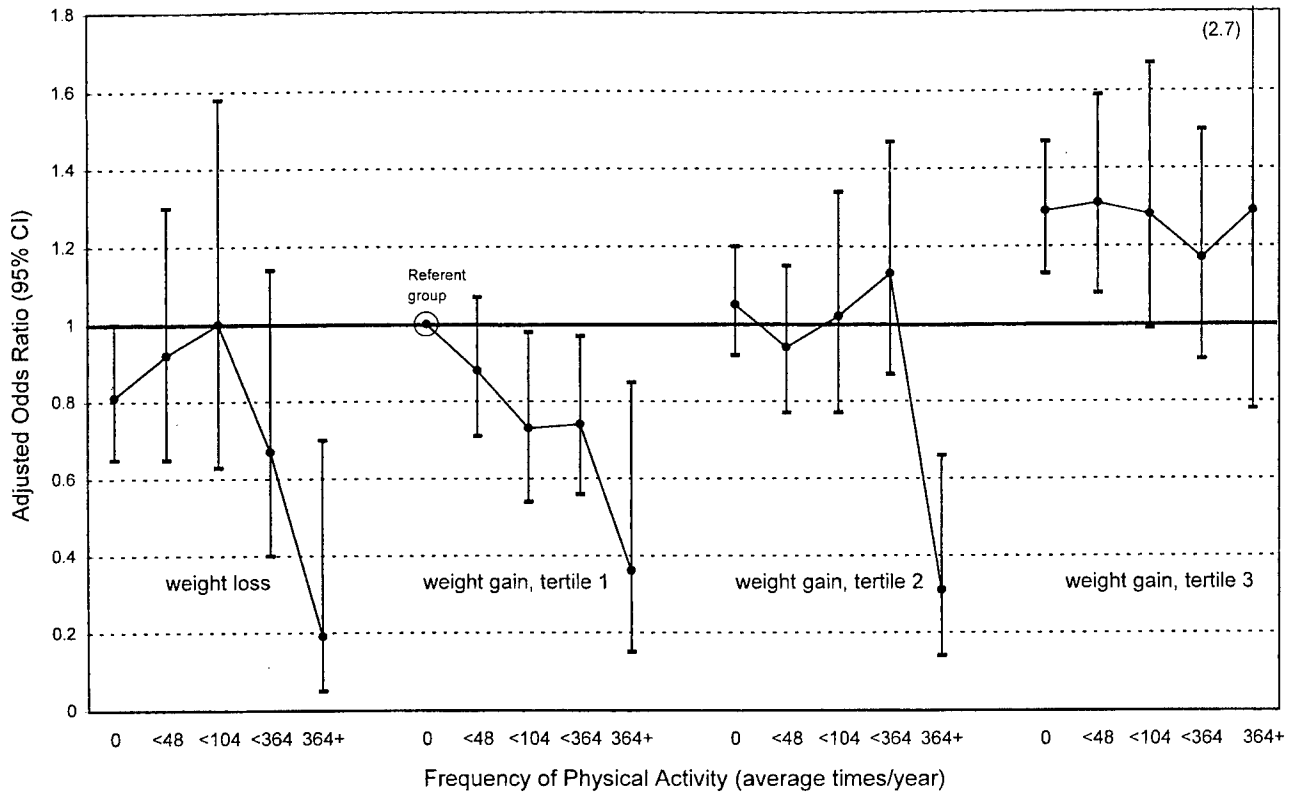

Fig. 2. Adjusted ORs of postmenopausal breast cancer according to weight change (weight at age 18 to recent weight) and frequency of physical activity at 14–22 years of age.

given the small sample size of this subgroup, this estimate is unstable. Interestingly, among women with little lifetime weight gain (first tertile), reduced risk of postmenopausal breast cancer was observed at lower frequencies of early-life activity, a pattern not observed in any other weight change subgroup. In the third tertile of weight gain, all OR estimates were >1.

Limitations of our study should be considered in the interpretation of results. High response rates of cases and controls make substantial selection bias unlikely. Our study's dependence on self-reports of past physical activity and body size makes it susceptible to recall bias (1). However, for a spurious inverse association to occur, physical activity would have to be underreported by cases or overreported by controls. Information was obtained on strenuous physical activity that occurred many years before the interview. Women's reports were reliable; in a reproducibility substudy of 203 women, the Spearman correlation coefficients between frequency of activity in the two interviews was found to be 0.60 (11). Similarly, Spearman correlation coefficients between reports of body size in two interviews indicated excellent reproducibility [weight at age 18, $r = 0.92$; recent weight, $r = 0.92$; height, $r = 0.95$ (14)]. Other studies have reported similar high levels of reliability and, to a lesser extent, validity (15, 16).

Our assessment of physical activity was limited to a single point in time and provided no information on duration or intensity. Whereas sparse data may have constrained our ability to identify a clear dose gradient, incomplete assessment of physical activity may also have contributed. It is possible that the group who exercised in early life and avoided weight gain is enriched with women who were relatively active throughout their lives. Thus, early-life activity may reflect later-life activity in this subgroup. Alternatively, weight gain may reflect inactivity after ages 14–22. A lifetime physical activity history, although challenging to obtain retrospectively, would provide more complete definitions of physical activity (17) and permit a full evaluation of timing of physical activity. We were unable to adjust for the potential confounding effect of later-life physical activity on breast cancer risk. Finally, weight change represents net change over many years; intermittent fluctuations were not assessed, nor was intentionality of weight change.

Evidence regarding an inverse association between activity and breast cancer generally supports a similar effect in postmenopausal women (1). However, the literature is less consistent in the period or periods that are most relevant. Results from two studies (11, 18) provide strong overall support of an inverse association between activity early in life and postmenopausal breast cancer (range, 50–54%), but other studies have not reported similar findings (19–22). The strong and adverse effect of weight gain on postmenopausal breast cancer (4, 14) may obscure any inverse associations between early-life physical activity and risk when evaluating an overall effect. To our knowledge, no studies have specifically evaluated how associations between physical activity during late adolescence/young adulthood and risk of postmenopausal breast cancer may differ according to early-life body size and subsequent weight change. Our results are in general agreement with a prospective study of Norwegian women (3) that included both pre- and postmenopausal women. In that study, Thune *et al.* (3) observed that the reduction in breast cancer risk associated with recreational physical activity, assessed 1 year before baseline,

was greatest in lean women (baseline BMI < 22.8 kg/m^2). For most subjects in this study, baseline assessment of physical activity and body size was at mid-life. Women in our study who lost weight (median change = −4.5 kg) or who gained small amounts (first tertile, median weight gain = 4.5 kg) were also the lightest 5 years before interview (median recent BMI = 20.7 and 21.9 kg/m^2, respectively). If the Norwegian women in the first tertile of BMI were similar with respect to net weight change to the women in our study who lost weight or gained little, then the reduced risk of postmenopausal breast cancer in our study is also comparable.

In summary, these current findings suggest that frequent episodes of strenuous physical activity during young adulthood may have the greatest benefit for reducing postmenopausal breast cancer risk among women who avoid substantive weight gain during adult life–a recommendation for general health (23). In postmenopausal women who gain substantive adult weight, the benefits of frequent and strenuous early-life physical activity appear to be lost. Unfortunately, the prevalence of recreational physical activity in this country is low (24, 25), and adult weight gain is increasingly common (26)–behaviors that may have contributed to breast cancer incidence.

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Appendix D: Tables showing results from reliability sub-study of intentional weight loss.

Table 1. Kappas (and 95% lower confidence limits) of the intentional weight loss questions among breast cancer cases and population controls, Wisconsin 1998-1999

Intentional weight loss of at least 10 pounds (Yes vs No)	Cases N=118	Controls N=82
Ever	0.70 (0.56)	0.73 (0.57)
In teens	0.80 (0.64)	0.68 (0.45)
In 20s	0.62 (0.45)	0.49 (0.27)
In 30s	0.53 (0.37)	0.50 (0.29)
In 40s	0.50 (0.31)	0.48 (0.27)
In 50s	0.73 (0.57)	0.51 (0.28)
In 60s*	0.29 (0)	0.72 (0.35)
In the previous decade	0.56 (0.41)	0.62 (0.45)

*The average age of the reliability sub-study participants was 54 years (range 32-68), so that the number of cases (N=2) and controls (N=3) in the sub-study who reported intentional weight loss in their sixties was limited.

TABLE 2: Kappas (and 95% confidence intervals) of the intentional weight loss methods reported by breast cancer cases and controls, Wisconsin, 1998-1999

Weight loss method*	Cases (N=118)	Controls (N=76)
Low calorie diet	0.46 (0.33, 0.59)	0.42 (0.26, 0.59)
Low fat diet	0.39 (0.25, 0.52)	0.52 (0.35, 0.69)
Skipped meals	0.60 (0.47, 0.73)	0.53 (0.35, 0.70)
Diet pills	0.66 (0.53, 0.80)	0.63 (0.46, 0.81)
Commercial weight loss program	0.69 (0.58, 0.80)	0.76 (0.63, 0.88)
Prescription medications	0.67 (0.54, 0.80)	0.54 (0.37, 0.71)
Exercise	0.49 (0.36, 0.62)	0.62 (0.47, 0.77)
High protein/low carbohydrate diet	0.63 (0.49, 0.77)	0.64 (0.47, 0.81)

*Each method categorized as 1) no intentional weight loss, 2) intentional weight loss using this method, and 3) intentional weight loss not using this method.

Appendix E: Tables describing relations between intentional weight loss and breast cancer risk.

TABLE 1. Selected characteristics of women with breast cancer (n=2,156) and population controls (n=2,833) according to intentional weight loss status.

	Intentional Weight Loss Status							
	Cases				Controls			
	Never		Ever		Never		Ever	
	N	%	N	%	N	%	N	%
Age (years)								
< 45	132	15.1	243	19.0	194	17.6	341	19.7
45 - 49	147	16.8	198	15.5	151	13.7	329	19.0
50 - 54	127	14.5	236	18.4	133	12.1	279	16.1
55 - 59	133	15.2	217	16.9	161	14.6	281	16.2
60 - 64	137	15.7	177	13.8	188	17.0	242	14.0
65 - 69	199	22.7	210	16.4	276	25.0	258	14.9
Recent body mass index (kg/m^2)								
< 22.0	313	35.8	158	12.3	410	37.2	186	10.7
22.0 - 24.0	209	23.9	206	16.1	261	23.7	273	15.8
24.1 - 26.4	147	16.8	246	19.2	197	17.9	338	19.5
26.5 - 29.5	134	15.3	289	22.6	141	12.8	433	25.0
≥ 29.6	67	7.7	372	29.0	83	7.5	480	27.8
Unknown	5	0.6	10	0.8	11	1.0	20	1.2
Weight change (kg)*								
< 0	66	7.5	89	6.9	88	8.0	115	6.6
0 - 6.4	245	28.0	186	14.5	328	29.7	262	15.1
6.5 - 13.1	235	26.9	254	19.8	294	26.7	377	21.8
13.2 - 20.9	186	21.3	316	24.7	217	19.7	433	25.0
> 20.9	129	14.7	407	31.8	157	14.2	495	28.6
Unknown	14	1.6	29	2.3	19	1.7	48	2.8

TABLE 1, continued. Selected characteristics of women with breast cancer (n=2,156) and population controls (n=2,833) according to intentional weight loss status.

	Intentional Weight Loss Status							
	Cases				Controls			
	Never		Ever		Never		Ever	
	N	%	N	%	N	%	N	%
Menopausal status								
Premenopausal	338	38.6	565	44.1	412	37.4	774	44.7
Postmenopausal	227	25.9	374	29.2	300	27.2	529	30.6
Unknown	310	35.4	342	26.7	391	35.4	427	24.7
Family history of breast cancer								
No	756	86.4	1104	86.2	1021	92.6	1547	89.4
Yes	103	11.8	166	13.0	66	6.0	143	8.3
Unknown	16	1.8	11	0.8	16	1.4	40	2.3
Parity								
0	251	28.7	322	25.2	262	23.8	379	21.9
1 - 2	252	28.8	403	31.5	273	24.8	523	30.3
3 - 4	180	20.6	280	21.9	257	23.3	400	23.1
≥ 5	192	21.9	274	21.4	310	28.1	427	24.7

* Weight change calculated as the difference between recent weight and weight at age 18.

TABLE 2. Odds ratios (95% CI) of breast cancer according to intentional weight loss at each age period.

Age Period of Intentional Weight Loss	Cases		Controls		Age-adjusted		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†	OR†	95% CI†
Overall								
Never intentionally lost	875	40.6	1103	38.9	1		1	
Lost weight at least once	1281	59.4	1730	61.1	0.93	0.83-1.04	0.94	0.82-1.06
Teens								
Never intentionally lost	875	40.8	1103	39.3	1		1	
No intentional weight loss at this age	1045	48.7	1357	48.3	0.96	0.85-1.09	0.97	0.85-1.11
Lost weight at least once	224	10.5	347	12.4	0.81	0.67-0.98	0.78	0.64-0.96
Twenties								
Never intentionally lost	875	41.0	1103	39.4	1		1	
No intentional weight loss at this age	819	38.3	1102	39.4	0.93	0.82-1.05	0.94	0.82-1.08
Lost weight at least once	441	20.7	594	21.2	0.94	0.81-1.10	0.94	0.79-1.11
Thirties								
Never intentionally lost	865	40.9	1071	39.5	1		1	
No intentional weight loss at this age	702	33.2	970	35.8	0.89	0.78-1.02	0.90	0.78-1.03
Lost weight at least once	547	25.9	670	24.7	1.00	0.87-1.16	1.03	0.87-1.20
Forties								
Never intentionally lost	791	41.2	987	40.0	1		1	
No intentional weight loss at this age	609	31.8	789	31.9	0.96	0.83-1.11	0.93	0.81-1.09
Lost weight at least once	518	27.0	694	28.1	0.92	0.79-1.07	0.91	0.77-1.08

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status and family history of breast cancer.

† OR, odds ratio; CI, confidence interval.

TABLE 2, continued. Odds ratios (95% CI) of breast cancer according to intentional weight loss at each age period.

Age Period of Intentional Weight Loss	Cases		Controls		Age-adjusted		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†	OR†	95% CI†
Fifties								
Never intentionally lost	557	42.8	714	43.0	1		1	
No intentional weight loss at this age	421	32.3	523	31.5	1.02	0.86-1.21	0.97	0.81-1.16
Lost weight at least once	325	24.9	424	25.5	0.97	0.81-1.17	0.92	0.75-1.12
Sixties								
Never intentionally lost	306	48.0	387	48.3	1		1	
No intentional weight loss at this age	216	33.9	267	33.3	1.02	0.81-1.29	0.93	0.72-1.19
Lost weight at least once	115	18.1	147	18.4	0.99	0.74-1.31	0.89	0.65-1.21
Recent								
Never intentionally lost	875	45.6	1103	43.6	1		1	
No intentional weight loss at this age	868	45.2	1179	46.6	0.92	0.81-1.04	0.91	0.79-1.04
Lost weight at least once	177	9.2	246	9.7	0.89	0.72-1.11	0.90	0.72-1.13

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status and family history of breast cancer.

† OR, odds ratio; CI, confidence interval.

TABLE 3. Odds ratios (95% CI) of breast cancer in women who ever intentionally lost weight, according to number of episodes of intentional weight loss at each age period.

Age Period of Intentional Weight Loss	Cases		Controls		Age-adjusted		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†	OR†	95% CI†
Teens								
No intentional weight loss at this age	1045	82.3	1357	79.6	1		1	
1 time	133	10.5	216	12.7	0.80	0.64-1.02	0.78	0.61-0.98
2 times	34	2.7	66	3.9	0.69	0.45-1.05	0.65	0.42-0.99
≥ 3 times	58	4.6	65	3.8	1.19	0.83-1.72	1.13	0.77-1.64
Twenties								
No intentional weight loss at this age	819	65.0	1102	65.0	1		1	
1 time	255	20.2	336	19.8	1.06	0.88-1.29	1.03	0.85-1.26
2 times	93	7.4	130	7.7	1.01	0.76-1.34	0.99	0.74-1.33
3 times	41	3.3	57	3.4	1.01	0.67-1.53	1.00	0.65-1.52
≥ 4 times	52	4.1	71	4.2	1.03	0.71-1.50	1.01	0.69-1.48
Thirties								
No intentional weight loss at this age	702	56.2	970	59.2	1		1	
1 time	334	26.7	373	22.7	1.25	1.05-1.50	1.29	1.08-1.55
2 times	109	8.7	157	9.6	1.00	0.77-1.31	1.05	0.80-1.38
3 times	49	3.9	58	3.5	1.19	0.80-1.76	1.24	0.83-1.85
≥ 4 times	55	4.4	82	5.0	0.95	0.66-1.36	0.94	0.65-1.35
Forties								
No intentional weight loss at this age	609	54.0	789	53.2	1		1	
1 time	338	30.0	455	30.7	0.97	0.81-1.15	0.99	0.82-1.18
2 times	98	8.7	132	8.9	0.99	0.74-1.31	1.02	0.77-1.37
≥ 3 times	82	7.3	107	7.2	1.00	0.74-1.37	0.98	0.72-1.35

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status and family history of breast cancer.

† OR, odds ratio; CI, confidence interval.

TABLE 3, continued. Odds ratios (95% CI) of breast cancer in women who ever intentionally lost at least 10 pounds, according to number of episodes of intentional weight loss at each age period.

Age Period of Intentional Weight Loss	Cases		Controls		Age-adjusted		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†	OR†	95% CI†
Fifties								
No intentional weight loss at this age	421	56.4	523	55.2	1		1	
1 time	231	31.0	306	32.3	0.94	0.76-1.17	0.94	0.76-1.18
2 times	54	7.2	79	8.3	0.86	0.59-1.24	0.85	0.58-1.24
≥ 3 times	40	5.4	39	4.1	1.30	0.82-2.05	1.24	0.77-1.99
Sixties								
No intentional weight loss at this age	216	65.3	267	64.5	1		1	
≥ 1 time	115	34.7	147	35.5	0.97	0.71-1.31	0.96	0.71-1.31
Recent								
No intentional weight loss at this age	868	83.1	1179	82.7	1		1	
≥ 1 time	177	16.9	246	17.3	0.98	0.79-1.21	0.99	0.80-1.23
Cumulative								
1 time	533	42.2	703	41.9	1		1	
2 times	258	20.4	355	21.1	0.97	0.79-1.18	0.98	0.80-1.20
3 times	135	10.7	215	12.8	0.84	0.65-1.07	0.86	0.67-1.11
4 times	107	8.5	110	6.6	1.29	0.96-1.72	1.32	0.98-1.78
5 times	59	4.7	69	4.1	1.16	0.81-1.68	1.21	0.83-1.76
≥ 6 times	171	13.5	227	13.5	1.00	0.80-1.26	1.00	0.79-1.27

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status and family history of breast cancer.

† OR, odds ratio; CI, confidence interval.

TABLE 4. Odds ratios (95% CI) of breast cancer in women who ever intentionally lost at least 10 pounds according to the total amount of weight lost at each age period.

Weight Loss (pounds)	Cases		Controls		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†
Teens						
0	1045	82.7	1357	80.0	1	
10 - 29	120	9.5	180	10.6	0.57	0.38-0.85
30 - 59	68	5.4	122	7.2	0.35	0.19-0.67
≥ 60	30	2.4	37	2.2	0.43	0.19-0.99
						p-trend=0.26‡
Twenties						
0	819	65.8	1102	65.3	1	
10 - 19	140	11.2	173	10.3	1.05	0.78-1.41
20 - 39	163	13.1	213	12.6	0.95	0.67-1.36
40 - 69	81	6.5	141	8.4	0.69	0.41-1.16
≥ 70	42	3.4	59	3.5	0.86	0.44-1.69
						p-trend=0.21‡
Thirties						
0	702	56.6	970	59.7	1	
10 - 19	174	14.0	174	10.7	1.43	1.08-1.89
20 - 39	203	16.4	253	15.6	1.23	0.90-1.68
40 - 69	118	9.5	160	9.9	1.11	0.71-1.75
≥ 70	43	3.5	67	4.1	0.94	0.53-1.68
						p-trend=0.03‡
Forties						
0	609	54.5	789	53.7	1	
10 - 19	181	16.2	241	16.4	0.92	0.68-1.24
20 - 39	202	18.1	228	15.5	1.01	0.69-1.46
40 - 69	84	7.5	147	10.0	0.60	0.36-1.00
≥ 70	41	3.7	64	4.4	0.64	0.34-1.17
						p-trend=0.07‡

TABLE 4, continued. Odds ratios (95% CI) of breast cancer in women who ever intentionally lost at least 10 pounds according to the total amount of weight lost at each age period.

Weight Loss (pounds)	Cases		Controls		Multivariable-adjusted*	
	N	%	N	%	OR†	95% CI†
Fifties						
0	421	57.0	523	55.4	1	
10 - 19	106	14.3	170	18.0	0.88	0.60-1.29
20 - 39	133	18.0	164	17.4	1.16	0.74-1.84
≥ 40	79	10.7	87	9.2	1.35	0.74-2.49
						p-trend=0.95‡
Sixties						
0	216	65.3	267	64.5	1	
10 - 29	77	23.3	104	25.1	0.95	0.67-1.35
≥ 30	38	11.5	43	10.4	1.00	0.61-1.62
						p-trend=0.96‡
Cumulative						
10 - 19	312	25.0	396	23.8	1	
20 - 29	194	15.6	279	16.8	0.86	0.68-1.10
30 - 39	164	13.2	224	13.5	0.92	0.70-1.19
40 - 49	122	9.8	147	8.8	1.01	0.74-1.38
50 - 69	160	12.8	205	12.3	0.89	0.65-1.21
70 - 89	91	7.3	123	7.4	0.82	0.56-1.21
90 - 119	88	7.1	101	6.1	0.87	0.57-1.34
≥ 120	115	9.2	189	11.4	0.57	0.37-0.89
						p-trend=0.01‡

* Multivariable models include age, recent BMI (5 levels), state, parity (4 levels), menopausal status, family history of breast cancer and number of times lost weight during the same decade.
† OR, odds ratio; CI, confidence interval.
‡ p-trend based on continuous variable.

TABLE 5. Odds ratios* and 95% confidence intervals of breast cancer according to cumulative weight loss in strata of weight change. †

Cumulative weight loss (pounds)	WEIGHT CHANGE (kg) < 0		0 - 8.6		8.7 - 17.7		> 17.7	
	case/control	OR, CI	case/control	OR, CI	case/control	OR, CI	case/control	OR, CI
10 - 19	36 / 49	1	89 / 117	1	96 / 144	1	100 / 94	1
20 - 29			42 / 73	0.72, 0.44-1.18	70 / 97	1.07, 0.70-1.64	66 / 84	0.74, 0.48-1.15
30 - 39	18 / 20	1.20, 0.50-2.88	42 / 51	1.03, 0.60-1.77	43 / 51	1.31, 0.78-2.20	65 / 112	0.58, 0.38-0.90
40 - 49			20 / 29	0.79, 0.38-1.63	29 / 43	1.10, 0.59-2.02	59 / 55	1.07, 0.65-1.76
50 - 69	33 / 40	0.97, 0.36-2.57 P-trend=0.98‡	25 / 48	0.52, 0.26-1.05	42 / 57	1.07, 0.56-2.04	73 / 85	0.84, 0.52-1.37
70 - 119			29 / 38	0.63, 0.26-1.55	40 / 61	0.92, 0.43-1.98	100 / 102	0.95, 0.56-1.61
≥ 120			12 / 25	0.39, 0.12-1.26 P-trend=0.29‡	25 / 34	1.00, 0.37-2.68 P-trend=0.37‡	64 / 117	0.51, 0.27-0.98 P-trend=0.04‡

* Odds ratios adjusted for age, BMI at age 18 (continuous), state, parity (4 levels), menopausal status, family history of breast cancer, and cumulative number of times weight was intentionally lost.

† Weight change is difference in recent weight and weight at age 18.

‡ P-trend based on continuous variable.

TABLE 6: Odds ratios (95% CI) of breast cancer according to methods of intentional weight loss

	Cases		Controls			
Weight Loss Method†	N	%	N	%	OR*	95% CI
Never intentionally lost weight	941	40.8	1142	39.4	1	
Low calorie diet						
Never	538	23.3	726	25.1	0.93	0.80-1.08
Ever	830	35.9	1030	35.5	0.99	0.87-1.14
Low fat diet						
Never	1144	49.5	1456	50.2	0.97	0.85-1.10
Ever	224	9.7	300	10.4	0.97	0.79-1.18
Skipped meals						
Never	1222	52.9	1550	53.5	0.97	0.85-1.10
Ever	146	6.3	206	7.1	0.93	0.73-1.18
Diet pills						
Never	1319	57.1	1689	58.3	0.97	0.86-1.10
Ever	49	2.1	67	2.3	0.88	0.59-1.30
Commercial weight loss program						
Never	853	36.9	1082	37.3	0.97	0.85-1.11
Ever	515	22.3	674	23.3	0.96	0.82-1.12
Prescription medications						
Never	1248	54.0	1068	55.5	0.96	0.85-1.09
Ever	120	5.2	148	5.1	1.04	0.79-1.35
Exercise						
Never	926	40.1	1145	39.5	0.99	0.86-1.13
Ever	442	19.1	611	21.1	0.93	0.79-1.09
High protein/low carbohydrate diet						
Never	1315	57.0	1696	58.5	0.96	0.85-1.09
Ever	53	1.8	60	2.1	1.14	0.77-1.68

*OR, odds ratio; CI, confidence interval. Multivariable models include age, state, body mass index, parity, menopausal status, and family history.

†Methods not shown were reported by <1% of subjects: laxatives or water pills, gastric surgery, and regurgitation.

TABLE 7: Odds ratios (95% CI)* of breast cancer according to method of intentional weight loss and weight change since age 18

Method of weight loss	Lost weight/no gain (≤0)		Gained (0-19)		Gained (20-39)		Gained (40+)	
	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)
Never lost	941/1142	1	941/1142	1	941/1142	1	941/1142	1
Low calorie diet								
Never	63/97	0.84 (0.59-1.16)	129/157	0.98 (0.75-1.26)	153/226	0.80 (0.63-1.02)	193/246	0.97 (0.75-1.25)
Ever	101/125	0.93 (0.70-1.24)	183/281	0.77 (0.63-0.96)	222/281	0.95 (0.77-1.18)	324/343	1.16 (0.92-1.46)
Commercial weight loss program								
Never	118/162	0.87 (0.68-1.13)	210/326	0.77 (0.63-0.94)	243/297	0.97 (0.79-1.19)	282/297	1.14 (0.90-1.44)
Ever	46/60	0.96 (0.64-1.44)	102/112	1.08 (0.81-1.44)	132/210	0.76 (0.59-0.98)	235/292	1.00 (0.78-1.28)
Exercise								
Never	113/150	0.91 (0.69-1.19)	198/265	0.89 (0.72-1.09)	253/338	0.86 (0.72-1.08)	362/392	1.11 (0.89-1.30)
Ever	51/72	0.85 (0.58-1.25)	114/173	0.78 (0.60-1.01)	122/169	0.90 (0.69-1.17)	155/197	1.00 (0.76-1.32)

*OR, odds ratio; CI, confidence interval. Multivariable models include age, state, body mass index, parity, menopausal status, and family history.
†Methods not shown were reported by <1% of subjects: laxatives or water pills, gastric surgery, and regurgitation.

TABLE 8: Odds ratios (95% CI) of breast cancer according to methods of intentional weight loss and average weight loss per episode

	Average weight loss per episode (pounds)			
	10-19		20+	
Method of intentional weight loss	Cases/Controls	OR (95% CI)*	Cases/Controls	OR (95% CI)*
Never	941/1142	1	941/1142	1
Low calorie diet				
Never	347/445	0.97 (0.81-1.15)	166/230	0.86 (0.68-1.09)
Ever	592/684	1.05 (0.90-1.21)	230/340	0.81 (0.66-1.00)
Commercial weight loss program				
Never	624/725	1.04 (0.90-1.20)	198/305	0.78 (0.63-0.97)
Ever	315/404	0.97 (0.80-1.16)	198/265	0.90 (0.71-1.14)
Exercise				
Never	629/704	1.08 (0.93-1.25)	267/388	0.80 (0.65-0.98)
Ever	310/425	0.90 (0.75-1.08)	129/182	0.90 (0.69-1.17)

*OR, odds ratio; CI, confidence interval. Multivariable models include age, state, body mass index, parity, menopausal status, and family history.
†Methods not shown were reported by <1% of subjects: laxatives or water pills, gastric surgery, and regurgitation.

TABLE 9: Odds ratios (95% CI) of breast cancer according to methods and timing of intentional weight loss

	Time period of intentional weight loss					
	Teens		20s		Recent	
Method of weight loss	Cases/Controls	OR (95% CI)*	Cases/Controls	OR (95% CI)*	Cases/Controls	OR (95% CI)*
Never	941/1142	1	941/1142	1	941/1142	1
Low calorie diet						
Never	85/123	0.80 (0.59-1.16)	180/237	0.99 (0.76-1.29)	74/105	0.69 (0.45-1.06)
Ever	151/217	0.86 (0.68-1.08)	278/354	0.98 (0.82-1.19)	70/94	1.05 (0.81-1.46)
Commercial weight loss program						
Never	222/320	0.87 (0.69-1.11)	386/483	1.02 (0.84-1.23)	102/131	0.94 (0.67-1.30)
Ever	14/20	0.79 (0.57-1.09)	72/108	0.92 (0.72-1.18)	42/64	0.95 (0.67-1.35)
Exercise						
Never	186/260	0.84 (0.66-1.08)	323/425	0.99 (0.81-1.21)	97/125	0.98 (0.71-1.35)
Ever	50/80	0.85 (0.62-1.14)	135/166	0.98 (0.79-1.23)	47/70	0.90 (0.63-1.28)

*OR, odds ratio; CI, confidence interval. Multivariable models include age, state, body mass index, parity, menopausal status, and family history.
†Methods not shown were reported by <1% of subjects: laxatives or water pills, gastric surgery, and regurgitation.

Appendix F

Recreational Physical Activity and Risk of Endometrial Cancer

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ABSTRACT

It is not known whether physical activity reduces the risk of developing endometrial cancer. Data from a population-based case-control study of Wisconsin women were used to evaluate associations between physical activity at three time periods and risk of endometrial cancer. Cases (n=745) were identified from a statewide tumor registry; controls (n=2,408) were selected randomly from population lists. Frequency of participation in moderate and vigorous activity at age 12, age 20 and five years prior to the reference date, and other factors were ascertained through telephone interviews. Odds ratios (OR) and 95% confidence intervals (CI) were computed using unconditional logistic regression and were adjusted for physical activity at other time periods, age, body mass index, smoking status, postmenopausal hormone use, parity and education. For physical activity at age 12, non-significant reductions in risk were observed for participation in moderate activities (OR=0.87, CI=0.64-1.18) or in any vigorous activities (OR=0.85, CI=0.62-1.18) compared to no activity. Physical activity at age 20 was not associated with endometrial cancer risk. Recent moderate and vigorous physical activity were associated with a 22% and 29% reduction in risk, respectively (moderate OR=0.78, CI=0.63-0.95; vigorous OR=0.71, CI=0.52-0.97). These data suggest that recent activity is associated with a decreased risk of endometrial cancer.

Keywords: physical activity, endometrial cancer
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Physical activity is hypothesized to lower circulating estrogen levels through several mechanisms (1-11). Because endometrial cancer is an estrogen-dependent cancer (12, 13), it follows that physical activity may confer protection against this disease through its direct effect on estrogen levels or indirectly through other means (14, 15). Recreational physical activity has been associated with decreased risk of endometrial cancer in several (16-19), but not all (20, 21) case-control studies. Risk reductions between 40% and 88% have been reported for various measures of activity and age periods. The purpose of this study is to contribute to the limited literature on physical activity and endometrial cancer risk by evaluating frequency of moderate and vigorous recreational physical activity assessed at several time periods, in a large, population-based case-control study of endometrial cancer.

MATERIALS AND METHODS

Participants

All participants were female residents of Wisconsin aged 40-79 years. Incident cases of invasive endometrial cancer (diagnosed between January 1, 1991 and December 31, 1994) were identified by a statewide mandatory cancer registry. According to an institutionally approved protocol, we contacted the physician of record for each eligible case by mail to obtain permission to approach the subject. Eligibility was limited to cases with listed telephone numbers, drivers' licenses verified by self-report (if less than 65 years of age), and Medicare cards (if more than 65 years of age). The reasons for nonparticipation included physician refusal (n=6), subject refusal (n=53), failure to locate (n=2) and death (n=50). A total of 745 cases (87 percent of those eligible) were interviewed. Of those cases interviewed, 98 percent had histologic confirmation of invasive endometrial cancer.

Community controls were selected randomly from lists of licensed drivers (if 40-64 years of age) and Medicare beneficiary files compiled by the health Care Financing Administration (if 65-79 years of age) as part of a larger, concomitant study of breast cancer (22). Controls were selected to yield an age distribution similar to that of the cases and met the eligibility criterion of having a listed telephone number. Controls were eligible for this study if they reported no previous diagnosis of endometrial cancer.

Reasons for nonparticipation among the 4,362 eligible controls included subject refusal (n=521), failure to locate (n=35) and death (n=88). Thus, a total of 3,718 control women (85.2 percent) completed the study interview. After they were interviewed, 1,304 controls who reported a history of hysterectomy and six for whom interviews were determined to be unreliable, were excluded. In all, data on 2,408 controls were available for analysis.

Data collection

Before subjects were contacted by telephone, cases and controls received letters briefly introducing the study. The 45-minute structured interview elicited information on numerous factors prior to an assigned reference date. For cases, it was the date of diagnosis of endometrial cancer. For comparability, controls were assigned a reference date that corresponded to the average date of diagnosis for similarly aged cases (within 5-year strata) interviewed during the same month. Trained study staff conducted telephone interviews without prior knowledge of subjects' disease status. The interviewer remained unaware of the subject's case-control status until the interview ended for 82% of cases and 96% of controls.

Recreational physical activity was assessed for three time periods: age 12, age 20 and 5 years prior to the reference date ("recent" activity) and at two levels, vigorous and moderate. Frequency of vigorous activity was assessed by asking subjects how often they participated in "...vigorous physical activities, like running, basketball, lap swimming or gymnastics". Moderate activity was assessed by asking subjects how often they participated in "...moderate physical activities like recreational volleyball, softball, brisk walking or leisurely biking". Vigorous activities correspond approximately to metabolic equivalency scores (METs) of 7-12 and moderate activities correspond to METs of 4-6 (23). Subjects were asked about their height at age 20 and about their weight and height prior to the assigned reference date ("recent" weight and height). The interview also covered reproductive experiences, exogenous hormone use, medical history, selected dietary factors, smoking history, and demographic factors.

Analyses

Frequency of moderate and vigorous activity at each time period was expressed as the number of times per week subjects engaged in physical activity. These continuous variables were dichotomized to reflect no activity and any activity within each time period. For each time period, dichotomous moderate and vigorous activity variables were cross-classified to represent no activity, only moderate activity and any vigorous activity. The 'any vigorous activity' group includes women who reported both vigorous and moderate activity or reported vigorous activity alone. For each time period, total frequency of activity was computed as the sum of frequencies of moderate and vigorous activity. This variable was used to evaluate tests for trend within the 'any vigorous activity' group. Body mass index (BMI) was computed using recent weight and maximum height (weight (kg) / height^2 (m^2)) and categorized into quintiles based on the control distribution.

Unconditional logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI) (24). Odds ratios were adjusted for activity at other time periods by including the relevant categorical variables in the model (no activity/moderate only/any vigorous). The models also included terms for established and potential risk factors including quintiles of BMI, age (continuous), smoking status (never, former, current), postmenopausal hormone use (never, former, current), parity (four levels), and education (four levels). Continuous physical activity (times per week) variables were included in models to evaluate tests for trend. Subjects with missing or incomplete information on individual physical activity variables were excluded from corresponding analyses (age 12: 29 cases, 135 controls; age 20: 16 cases, 68 controls; recent: 6 cases, 43 controls) . Women with missing values for covariates were assigned to unknown categories and retained in all analyses.

RESULTS

As expected, compared to the controls, women with endometrial cancer were more likely to be of greater body size, users of postmenopausal hormone therapy, current smokers, and nulliparous (Table 1). These variables, plus education, were therefore included as potential confounders in all regression models.

Age- and multivariable-adjusted odds ratios of endometrial cancer according to participation in moderate and vigorous activity at each age period compared to no activity are presented in Table 2. Although moderate activity was common in all three time periods, the

percentage of women reporting vigorous activity dropped dramatically after age 12. At age 12, non-significant reductions in risk were observed for participation in moderate activities only or in any vigorous activity compared to no activity (OR=0.87, CI=0.64-1.18; OR=0.85, CI=0.62-1.18, respectively). At age 20, physical activity at either level was not associated with endometrial cancer.

Recent moderate and vigorous physical activity were associated with a significant 22% and 29% reduction in endometrial cancer risk, respectively, compared to no activity (OR= 0.78, CI=0.63-0.95; OR=0.71, CI=0.52-0.97). Within the moderate and vigorous groups, increasing frequency of activity was not associated with further reductions in risk (p-trends = 0.86 and 0.79, respectively).

Body size did not appear to modify the association between recent activity and endometrial cancer risk (Table 3), nor did use of postmenopausal hormone therapy. However, the data suggest that the association between recent activity and endometrial cancer was modified by smoking status (p=0.02) and parity (p=0.01). The inverse association between recent physical activity and endometrial cancer risk appeared strongest in women who never smoked (moderate only OR=0.63, CI=0.48-0.82; any vigorous OR=0.57, CI=0.38-0.85) and in women with five or more children (moderate only OR=0.53, CI=0.33-0.85; any vigorous OR=0.27, CI=0.11-0.70).

DISCUSSION

In this large study, recent physical activity was associated with a decreased risk of endometrial cancer, with the greatest reduction associated with participation in vigorous activity. However, no trend was observed with increasing frequencies of recent moderate or vigorous activity. At earlier ages, moderate and vigorous activity had minimal associations with endometrial cancer risk.

Limitations of our study should be considered when the interpreting the results. High response rates of cases and controls make substantial selection bias unlikely. However, recall bias may be present due to our study's dependence on self-reports of physical activity. Another potential limitation is the validity of physical activity assessment. We used brief standardized questions to assess frequency and intensity of activity. While these assessments were accompanied by examples of relevant types of activity, it was up to the respondent to summarize all activities that were perceived to be "moderate" or "vigorous". Our study also did not obtain information on duration of episodes of activity. Finally, although validity may be a potential limitation, the reports themselves are likely reliable. In a reproducibility sub-study of 182 control women (71% of eligible controls), intra-class correlation coefficients ranged between 0.29 and 0.67 for physical activity questions administered, on average, 3 months apart (range 2-6 months). Other studies have reported similar levels of reproducibility (25-28).

In general, our results are in agreement with other studies (16-19). In a study of female residents of Hawaii (16), a 40% reduction in endometrial cancer risk was observed for the second quartile of lifetime hours in leisure-time activity compared to the first quartile with no further reductions in risk for higher levels of activity (p-trend = 0.34). Olson et al. (17) observed a 50% reduction in endometrial cancer risk associated with moderate levels of vigorous exercise (activity resulting in sweating) at age 16 and 20 years prior to interview. However, greater frequency of vigorous activity was not associated with a further reduction in risk. Also,

frequency of exercise was not significantly associated with endometrial cancer risk at time periods more proximate to interview. Sturgeon (19) observed that climbing stairs, but not participation in active sports or walking/hiking, was inversely associated with endometrial cancer risk. More general measures of activity, however, were not. Finally, in a hospital-based case-control study (18), the highest category of self-rated physical activity level was associated with large reductions in risk (58% - 88%) at various age periods.

Most studies, including ours, that observed reduced risks of endometrial cancer associated with a particular level of activity, did not find a dose-response relationship. In a study of Italian and Swiss women (18), however, dose-response associations were observed for each age period. In this study (18), activity was approximated using subjective reports (very low, moderately low, moderately high, high) of total physical activity at each age period. Determining whether higher levels of activity (frequency, intensity and/or duration) are associated with greater reductions will require further study with larger numbers of active women. Presently, assessing relations between high levels of activity and endometrial cancer risk is difficult to evaluate in a population-based setting because so few women are physically active (29). In our study, only 15% reported any recent vigorous activity.

In our data, the inverse association between recent physical activity and endometrial cancer risk was stronger in never smokers and highly parous women. We anticipated that the beneficial effect of physical activity would be greatest in women who had potentially higher unopposed estrogen exposure (e.g. high BMI, current users of postmenopausal hormones, never smokers). It is unclear why highly parous women exhibited a stronger relation with physical activity. It is possible that there are other characteristics of highly parous women that were not measured which confound the physical activity/endometrial cancer association observed in this sub-group. Overall, the hormone-related attributes of these effect modifiers lends support for the hypothesis that the physical activity and endometrial cancer association is also hormone-mediated. Others (18, 19) have noted interactions with body size, although Shu (21) did not observe differences in associations according to body size or parity.

In summary, these findings suggest that recent physical activity may reduce the risk of endometrial cancer. Our data are consistent with epidemiologic evidence supporting the importance of recent endogenous (30-33) and exogenous (34, 35) estrogen exposures. Physical activity during earlier life periods appears to have little association with risk of endometrial cancer. Future studies are necessary to more precisely determine how various elements of physical activity (frequency, intensity, duration) are associated with such factors as lifetime estrogen exposure, recent estrogen exposure and other relevant hormones, such as insulin (36), and how these associations impact the development of endometrial cancer.

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TABLE 1. Odds ratios of endometrial cancer in cases and population controls.*

Risk Factor	No. of cases	No. of controls	Age-adjusted odds ratio	95% confidence interval
Body mass index (kg/m^2)				
< 22.0	82	458	1.0	
22.1-24.2	99	461	1.19	0.86-1.64
24.3-26.6	106	458	1.28	0.94-1.76
26.7-30.1	157	463	1.91	1.41-2.57
> 30.1	281	457	3.49	2.64-4.61
Hormone therapy use (postmenopausal women only)				
Never	415	1603	1.0	
Former	181	428	1.61	1.31-1.97
Current	142	305	1.85	1.47-2.33
Smoking status				
Never	445	1273	1.0	
Former	226	725	0.90	0.74-1.08
Current	69	360	0.55	0.41-0.73
Parity				
0	123	253	1.0	
1-2	267	712	0.76	0.59-0.99
3-4	249	884	0.58	0.45-0.76
≥ 5	105	546	0.40	0.30-0.54
Education				
Less than high school	133	393	1.0	
High school graduate	362	1197	0.92	0.73-1.16
Some college	155	450	1.03	0.79-1.36
College graduate	90	301	0.90	0.66-1.23

* Sample sizes differ slightly due to missing values.

TABLE 2. Odds ratios (95% CI) of endometrial cancer according to participation in recreational activity at each age period.

Categories of Activity	Cases		Controls		Age-adjusted		Multivariable-adjusted*		P-trend, continuous variable‡
	N	%	N	%	OR†	95% CI†	OR†	95% CI†	
Age 12									
no activity	83	11.6	212	9.3	1.00		1.00		
moderate only	348	48.6	1092	48.0	0.79	0.60-1.05	0.87	0.64-1.18	0.87
any vigorous	285	39.8	969	42.7	0.73	0.54-0.97	0.85	0.62-1.18	0.40
Age 20									
no activity	261	35.8	814	34.8	1.00		1.00		
moderate only	376	51.6	1179	50.4	0.99	0.83-1.19	1.07	0.88-1.31	0.59
any vigorous	92	12.6	347	14.6	0.82	0.63-1.08	0.96	0.71-1.30	0.30
Recent									
no activity	228	30.8	568	24.0	1.00		1.00		
moderate only	420	56.8	1444	61.1	0.72	0.60-0.87	0.78	0.63-0.95	0.86
any vigorous	91	12.4	353	14.9	0.63	0.48-0.83	0.71	0.52-0.97	0.79

* Multivariable models include age, parity, menopausal status, smoking status, postmenopausal hormone use, education, recent BMI and categorical physical activity variables.

† OR, odds ratio; CI, confidence interval.

‡ From stratified analyses of the frequency of activity within each category of activity.

TABLE 3. Odds ratios* and 95% confidence intervals of endometrial cancer according to selected factors and their interaction with recent physical activity.

	Recent Activity			P for interaction†
	none	moderate only	any vigorous	
Body Mass Index (kg/m^2)				
≤ 23.5	1	0.66, 0.40-1.08	0.73, 0.39-1.36	
23.6-27.4	1	0.82, 0.54-1.25	0.71, 0.40-1.26	0.40
≥ 27.5	1	0.74, 0.57-0.98	0.62, 0.39-0.98	
Hormone Therapy Use				
Never	1	0.85, 0.66-1.10	0.63, 0.41-0.96	
Former	1	0.60, 0.38-0.95	0.63, 0.33-1.22	0.69
Current	1	0.74, 0.43-1.29	0.71, 0.36-1.39	
Smoking Status				
Never	1	0.63, 0.48-0.82	0.57, 0.38-0.85	
Former	1	0.97, 0.66-1.42	0.88, 0.51-1.52	0.02
Current	1	1.53, 0.78-3.02	1.22, 0.47-3.19	
Parity				
0	1	0.76, 0.43-1.35	1.31, 0.58-2.99	
1-2	1	0.86, 0.60-1.24	0.64, 0.38-1.07	0.01
3-4	1	0.79, 0.56-1.11	0.81, 0.49-1.33	
≥ 5	1	0.53, 0.33-0.85	0.27, 0.11-0.70	

* Odds ratios adjusted for age, parity, menopausal status, smoking status, use of hormone replacement therapy, education and recent body mass index.

† Evaluated continuously with total frequency where appropriate.

Appendix G

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Diabetes, Body Size, and Risk of Endometrial Cancer

Suzanne M. Shoff[1] and Polly A. Newcomb[1,2]

Data from a population-based case-control study of Wisconsin women were used to evaluate the relation of diabetes to the risk of endometrial cancer on the basis of body mass index (BMI). Cases (n = 723) were identified from a statewide tumor registry; controls (n = 2,291) were selected randomly from population lists. Diabetes status, weight, height, and other factors were ascertained by telephone interview. Subjects were categorized as not overweight (BMI, <29.1), overweight (BMI, 29.1–31.9), or obese (BMI, >31.9) according to the BMI distribution of middle-aged white women in the Second National Health and Nutrition Examination Survey. Joint associations between diabetes status, BMI, and endometrial cancer were evaluated using unconditional logistic regression models that controlled for age, parity, use of hormone replacement therapy, education, and smoking. Compared with persons without diabetes, those with diabetes had an adjusted odds ratio of 1.86 (95% confidence interval (CI) 1.37–2.52) for endometrial cancer. This association was modified by BMI (p interaction = 0.04). Compared with nonoverweight nondiabetic subjects, nonoverweight and overweight women who reported diabetes had nonsignificant elevated risks of endometrial cancer (nonoverweight, odds ratio (OR) = 1.10, CI 0.66–1.86; overweight, OR = 1.58, CI 0.81–3.05). In contrast, elevated risk estimates were observed for obese diabetic women (OR = 2.95, CI 1.60–5.46). These data contradict earlier reports and suggest that diabetes confers no additional risk of endometrial cancer in women who are neither overweight nor obese. *Am J Epidemiol* 1998;148:234–40.

body mass index; case-control studies; diabetes mellitus, non-insulin-dependent; endometrial neoplasms; logistic models; obesity in diabetes

Diabetes is hypothesized to be a risk factor for endometrial cancer, although epidemiologic data are inconclusive. Early studies reporting crude risk estimates (1–5) or simple percentages of incident cases with diabetes compared with the population prevalence of diabetes (6) generally show a greater prevalence of diabetes in subjects with this cancer, although results are not consistent (7–9). Studies that have adjusted for body mass report positive (10, 11) or null (12, 13) associations. Because non-insulin-dependent diabetes mellitus (NIDDM) is often associated with an elevated body size (14), and because body size consistently demonstrates strong positive associations with endometrial cancer (15), it is of interest to determine whether the relation between diabetes and endometrial cancer is due, in part, to associations with body size. If other metabolic characteristics of diabetes, such as hyperinsulinemia, have an etiologic role in endometrial cancer independent of body weight, as has been hypothesized for colorectal (16, 17) and breast (18, 19) cancers, then the risk associated with having diabetes should be evident in all strata of body weight. The aim of our analysis was to evaluate the modifying effect of body size on the relation between self-reported diabetes status and risk of endometrial cancer.

MATERIALS AND METHODS

Participants

All participants were female residents of Wisconsin aged 40–79 years. Incident cases of invasive endometrial cancer (diagnosed between 1991 and 1994) were identified by a statewide mandatory cancer registry. According to an institutionally approved protocol, we contacted the physician of record for each eligible case by mail to obtain permission to approach the subject. Eligibility was limited to cases with listed telephone numbers, drivers' licenses verified by self-report (if less than aged 65 years), and Medicare cards (if more than aged 65 years). A total of 745 cases (87 percent of those eligible) were interviewed. The reasons for nonparticipation included physician refusal (n = 6), subject refusal (n = 53), failure to locate (n = 2), and

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Abbreviations: BMI, body mass index; CI, confidence interval; NIDDM, non-insulin-dependent diabetes mellitus; OR, odds ratio.

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death ($n = 50$). Of those cases interviewed, 98 percent had histologic confirmation of invasive endometrial cancer.

Community controls were selected randomly from lists of licensed drivers (if less than aged 65 years) and Medicare beneficiary files compiled by the Health Care Financing Administration (if aged 65–79 years). The controls were selected at random to yield an age distribution similar to that of the cases, and the controls met the eligibility criterion of having a listed telephone number. Controls were eligible for the study if they reported no previous diagnosis of uterine cancer.

Of the 4,362 eligible controls, 521 (11.9 percent) refused to participate, 35 (0.8 percent) could not be located, and 88 (2.0 percent) were deceased. A total of 3,718 (85.2 percent) completed the study interview. After they were interviewed, 1,304 controls who reported a history of hysterectomy and six for whom interviews were determined to be unreliable were excluded. In all, data on 2,408 controls were available for analysis.

Data collection

Before they were contacted by telephone, cases and controls received letters briefly describing the study. The 45-minute structured interview elicited information on numerous factors prior to an assigned reference date. For cases, it was the date of diagnosis of endometrial cancer. For comparability, controls were assigned a reference date that corresponded to the average date of diagnosis for similarly aged cases (within 5-year strata) interviewed during the same month. Trained study staff conducted telephone interviews without prior knowledge of subjects' disease status. When interviewing 82 percent of the cases and 96 percent of the controls, the interviewer remained unaware of the subject's case-control status until the interview ended.

Diabetes status was ascertained by asking subjects whether, prior to the assigned reference date, their physician had ever told them that they had diabetes. Age at diabetes diagnosis was also queried. Subjects were asked about their height when they were in their twenties and about their weight and height prior to the assigned reference date, as well as about their minimum and maximum weights since age 20 years. In addition, the interview covered reproductive history, exogenous hormone use, medical history, smoking history, and demographic factors.

Information on diabetes status was missing for six cases and 67 controls; of the remaining subjects, data on weight and/or height were incomplete for 16 cases and 50 controls. Thus, for this analysis, complete information was available for 723 cases and 2,291 controls.

Analyses

Duration of diabetes was calculated as the difference between the subject's current age and age at diagnosis of diabetes. Those without diabetes were assigned a duration of 0. Duration was divided into tertiles based on the distribution of controls with diabetes. A fourth category of duration included three diabetic subjects (one case, two controls) who did not know their age at diagnosis. Body mass index (BMI) was computed using current weight and maximum height (weight (kg)/height^2 (m^2)). Subjects were categorized as not overweight (BMI, <29.1), overweight (BMI, 29.1–31.9), or obese (BMI, >31.9) according to the BMI distribution of middle-aged white women (aged 55–64 years) in the Second National Health and Nutrition Examination Survey of 1976–1980 (20). The lower and upper ends of the "overweight" category correspond to the 75th and 85th percentiles, respectively, of this population. Age was defined as the age at diagnosis or reference date. Parity was the sum of livebirths and stillbirths.

Multivariable logistic regression was used to compute odds ratios and 95 percent confidence intervals (21). The models included terms for established and potential risk factors including BMI, age (continuous), smoking status (never, former, current), use of hormone replacement therapy (never, former, current), parity (four levels), and education (four levels). The interaction between BMI and diabetes status was evaluated by including a term representing the product of the continuous BMI variable and the dichotomous diabetes variable. The model that includes indicator variables for joint classification of subjects according to diabetes status and BMI category also includes continuous BMI to control for residual confounding.

RESULTS

The prevalence of diabetes was significantly higher among cases (12 percent) than among controls (6 percent) (chi-square $p = 0.0001$). Cases were also significantly heavier than controls (mean BMI, 29.8 vs. 26.3 kg/m^2; Student's t test $p = 0.0001$).

Selected characteristics of cases and controls, according to diabetes status, are shown in table 1. Compared with controls who had diabetes, cases who had diabetes were heavier ($p = 0.0001$) and had a shorter duration of diabetes, although this latter difference was not statistically significant ($p = 0.13$). The ages of diabetic cases and controls were not different ($p = 0.45$).

Table 2 shows multivariable-adjusted odds ratios of endometrial cancer according to diabetes status, duration of diabetes, BMI category, and other covariates. Diabetes was associated with an almost twofold in-

TABLE 1. Selected characteristics (%) of women with endometrial cancer (n = 723) and population controls (n = 2,291) according to diabetes status,* Wisconsin, 1991–1994

	Diabetes status			
	Cases		Controls	
	Present (n = 87)	Absent (n = 636)	Present (n = 143)	Absent (n = 2,148)
Age (years)				
40–49	8	12	1	3
50–59	11	26	18	32
60–69	52	32	52	39
70–79	29	30	29	26
Mean†	64.8 (8.7)	62.6 (10.1)	65.7 (7.3)	63.1 (8.4)
Duration of diabetes (years)				
≤5	37		33	
6–13	38		34	
≥14	25		33	
Mean†	9.8 (9.0)	0	11.9 (10.4)	0
Body mass index (kg/m²)				
Not overweight	23	59	56	76
Overweight	18	13	22	12
Obese	59	28	22	12
Mean†	34.5 (7.0)	29.1 (7.4)	29.1 (5.5)	26.1 (5.0)

* For those subjects reporting a history of diabetes, 86 cases and 141 controls reported an age at diagnosis.
† Standard deviation in parentheses.

crease in risk of endometrial cancer (odds ratio (OR) = 1.86, 95 percent confidence interval (CI) 1.37–2.52). Duration of diabetes (compared with no diabetes) was associated with an increased risk of endometrial cancer that decreased as duration increased (p trend = 0.001). BMI was associated with a risk of endometrial cancer. Compared with having a low BMI (<29.1 kg/m^2), being overweight was associated with an odds ratio of 1.60 (95 percent CI 1.23–2.08), and obesity was associated with an almost fourfold increase in risk (OR = 3.88, 95 percent CI 3.11–4.85).

The association between diabetes and endometrial cancer was modified by BMI (p interaction = 0.04). To investigate this modifying effect further, joint associations between diabetes status and BMI category were evaluated (table 3). Compared with those who did not have diabetes and were not overweight, diabetics of moderate body size (BMI, <29.1) had a nonsignificant elevated risk (OR = 1.10, 95 percent CI 0.66–1.86). Overweight subjects with diabetes had a higher risk of endometrial cancer, although this association was not statistically significant (OR = 1.58, 95 percent CI 0.81–3.05). However, obese subjects with diabetes had a substantially increased risk (OR = 2.95, 95 percent CI 1.60–5.46). This odds ratio is greater than the expected joint effects estimated from the additive (1.10 + 1.15 − 1.0 = 1.25) and multiplicative (1.10 × 1.25 = 1.38) models.

DISCUSSION

Data presented here suggest that women with diabetes who are not obese have no increased risk of endometrial cancer compared with nonoverweight women without diabetes. For obese women, having diabetes is associated with an approximately threefold increase in risk above that attributed to body size alone.

In our study, the overall twofold increase in risk associated with diabetes is similar to risk estimates reported by others who adjusted for body size (10, 11). The prevalence of diabetes among cases in our population was similar to that reported by Brinton et al. (11) and Spengler et al. (5). Others have reported both a higher (1, 4, 10) and a lower (3, 7, 8, 13) prevalence of diabetes in their case populations. A limitation of most studies, including this one, is that the type of diabetes is not known. Among the diabetic subjects in our study, only 3.9 percent (one case, eight controls) reported that their diabetes was diagnosed before age 30 years; for 73 percent, it was diagnosed at age 50 years or older. Thus, the majority of this sample is likely composed of persons diagnosed with NIDDM. Excluding the early-onset subjects did not meaningfully alter the results (adjusted diabetes: OR = 1.96, CI 1.44–2.68). La Vecchia et al. (10) noted that an increased risk of endometrial cancer was apparent only for women with adult-onset diabetes (i.e., NIDDM).

Some limitations should be considered when interpreting our results. A high percentage of women participated in the study (87 percent of cases and 85 percent of controls), which suggests that selection bias, if any, was limited. However, nondiabetics may have been misclassified. It is estimated that about 50 percent of the population with diabetes is undiagnosed

TABLE 2. Odds ratios of endometrial cancer in cases (n = 723) and population controls (n = 2,291) according to diabetes status, duration of diabetes, body mass index, and other covariates, Wisconsin, 1991–1994

	Cases	Controls	Multivariable-adjusted OR*,†	95% CI*
Diabetes				
Absent	636	2,148	1.00	
Present	87	143	1.86	1.37–2.52
Duration of diabetes (years)				
0 (no diabetes)	636	2,148	1.00	
≤5	32	46	2.14	1.30–3.51
6–13	33	48	1.99	1.22–3.24
≥14	21	47	1.40	0.80–2.43
Body mass index (kg/m²)				
Not overweight	393	1,714	1.00	
Overweight	101	293	1.60	1.23–2.08
Obese	229	284	3.88	3.11–4.85
Smoking status				
Never	432	1,238	1.00	
Former	222	697	0.86	0.71–1.05
Current	69	356	0.62	0.46–0.83
Use of hormone replacement therapy				
Never	405	1,566	1.00	
Former	177	422	1.86	1.50–2.32
Current	141	303	2.49	1.94–3.20
Education				
Some high school	125	381	1.00	
Completed high school	355	1,176	0.80	0.62–1.04
Some college	153	442	0.89	0.66–1.20
≥4 years of college	90	292	0.74	0.53–1.05
Parity				
0	123	235	1.00	
1–2	263	674	0.77	0.59–1.02
3–4	239	855	0.51	0.39–0.68
≥5	98	527	0.31	0.23–0.43

* OR, odds ratio; CI, confidence interval.
† Estimates adjusted for age and other variables.

TABLE 3. Adjusted odds ratios* of endometrial cancer in cases (n = 723) and population controls (n = 2,291) by combined categories of body mass index and diabetes status,† Wisconsin, 1991–1994

Diabetes	Body mass index category											
	Not overweight				Overweight				Obese			
	Cases	Controls	OR‡	95% CI‡	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Absent	373	1,633	1		85	262	0.91	0.66–1.27	178	253	1.15	0.75–1.77
Present	20	81	1.10	0.66–1.86	16	31	1.58	0.81–3.05	51	31	2.95	1.60–5.46
p interaction = 0.04												

* Adjusted for body mass index (continuous), age (continuous), smoking status (never, former, current), education (categorical), parity (categorical), and use of hormone replacement therapy (never, former, current).
† Beta coefficients (standard errors) for indicator variables and interaction term: diabetes absent/overweight: −0.09 (0.17); diabetes absent/obese: 0.14 (0.22); diabetes present/not overweight: 0.10 (0.27); diabetes present/overweight: 0.45 (0.34); diabetes present/obese: 1.08 (0.31); diabetes status × continuous body mass index interaction term: 0.06 (0.03).
‡ OR, odds ratio; CI, confidence interval.

(22). Because study participants were sampled from the general population, it is likely that an appreciable number had diabetes but were unaware of their condition. In addition, because overweight and obese persons are more likely to have undiagnosed diabetes (23), the modifying effect of BMI may be partly attributable to misclassification of diabetes status among these participants.

Another limitation is that our results may reflect bias due to increased surveillance of persons with diabetes. A similar bias was posited by Horwitz and Feinstein (24), whereby women on hormone replace-

ment therapy were subject to increased surveillance that may have resulted in earlier detection of asymptomatic endometrial adenocarcinoma. To evaluate the possibility that diabetics were more likely to receive a diagnosis of endometrial cancer, we determined whether cases were diagnosed with an earlier stage of the disease if they were diabetic. A similar proportion of cases with diabetes (83 percent) and without diabetes (78 percent) were diagnosed with localized disease ($p = 0.4$). Thus, more frequent health surveillance of persons with diabetes is unlikely to have introduced bias into these analyses. Furthermore, there is no routine screening test for endometrial cancer; 90 percent of women with this cancer present with postmenopausal bleeding (25). Thus, increased surveillance is unlikely.

The strong interaction between BMI and diabetes observed in this study supports the hypothesis that hyperinsulinemia may be an etiologic factor in endometrial carcinogenesis, as has been proposed for other cancers (16–19, 26–29). Potischman et al. (30) have suggested that insulin may be a relevant factor in explaining the strong associations between body size, adiposity, and risk of endometrial cancer. They report that after controlling for endogenous sex hormones and sex hormone binding globulin, risk estimates for measures of body size and adiposity remained essentially the same, and they suggest that unopposed estrogen alone may not explain fully the body size/body fat associations with endometrial cancer. Interestingly, a subsequent investigation in this population using measurements of C-peptide (an indicator of insulin secretion) did not support an etiologic role of hyperinsulinemia (31). In women reporting no history of diabetes, no association was observed between C-peptide levels and risk of endometrial cancer after adjusting for BMI, waist-to-thigh ratio, and other factors (31).

Pathophysiologic levels of insulin may be causally related to endometrial cancer as a result of several interrelated mechanisms. Insulin may act as an endometrial mitogen by augmenting the proliferative effects of insulin-like growth factors (32–36). However, an understanding of the role of growth factors in endometrial carcinogenesis is incomplete (37), and data from human studies on the relation between hyperinsulinemia and the insulin-like growth factor system in the etiology of endometrial cancer remain inconclusive (38). Insulin may also operate through its associations with decreased levels of sex hormone binding globulin and increased levels of testosterone (29, 39–42), resulting in elevated levels of free estrogen. With regard to the hyperinsulinemia hypothesis, use of sulfonylureas, hypoglycemic agents that stimulate insulin secretion (43), is of interest.

The modifying effect of BMI on the relation between diabetes and endometrial cancer observed in this study may be a marker of some of the metabolic abnormalities that are highly correlated with body size and adiposity (44–46). NIDDM is the result of complex interactions between impaired insulin secretion, reduced glucose disposal in insulin-sensitive tissues, and dysregulation of hepatic glucose production (47). Large interindividual variation exists in the metabolic abnormalities that precede glucose intolerance and hyperglycemia. It is generally believed that insulin insensitivity with compensatory increases in insulin secretion precedes hyperglycemia and that prolonged hypersecretion of insulin leads to pancreatic beta cell dysfunction with a concomitant decrease in insulin secretion (47, 48). Insulin sensitivity (49) and insulin levels (50, 51) appear to vary according to body size, although there is much heterogeneity in this association (52). Thus, women with diabetes who are not obese may not have an increased risk of endometrial cancer, because they were not exposed to the same level of insulin as obese diabetic women. In our study, nonoverweight subjects reported significantly lower minimum and maximum weights since age 20 years compared with overweight and obese participants (data not shown). The lower weights maintained by nonoverweight diabetic subjects may have resulted in relatively lower levels of circulating insulin compared with overweight and obese diabetic subjects.

In this study, a long duration of diabetes ($\geq$14 years) was not associated with a risk of endometrial cancer. This finding is intriguing given the strong age-independent relation between duration and other chronic diseases (53–57). Concerning the insulin hypothesis, it may be expected that endometrial cancer risk would decrease with increasing duration given the inverse association between duration and insulin secretion in persons with NIDDM. Our data suggest this trend. However, meaningful associations would be difficult to detect without information on the use of hypoglycemic agents. These drugs act differently to reduce glucose levels (58), and mode of action may be relevant to circulating insulin levels. Alternatively, it is possible that among subjects with diabetes of long duration, weight loss associated with poor glycemic control may offset the adverse effects of other metabolic aspects of diabetes. In this study, a modest age-independent, inverse correlation between BMI and duration was statistically significant in diabetic subjects ($r = -0.23$, $p = 0.0005$).

Important characteristics of diabetes that may differ between cases and controls and may be related to weight, including measures of abdominal adiposity, use of hypoglycemic agents, levels of endogenous

insulin, and degree of glycemic control, could not be accounted for in our study. This limitation makes it difficult to separate the effects of weight from other metabolic aspects of diabetes when determining its relation to risk of endometrial cancer. Future studies will benefit from measuring these parameters where possible. Nevertheless, our data show that the relation of diabetes to endometrial cancer is modified by body size. For women who are not obese, diabetes itself appears to confer no additional risk.

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ATTENTION OF:

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1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports. Request the limited distribution statement for reports on the enclosed list be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

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PHYLIS M. RINEHART
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Information Management

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